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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
LIU, SAMUEL W

ART UNIT	PAPER NUMBER
1653	10

DATE MAILED: 06/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/774,814	BALLEVRE ET AL.	
	Examiner	Art Unit	
	Samuel W Liu	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-49* is/are pending in the application.

4a) Of the above claim(s) *45-49* is/are withdrawn from consideration.

5)☒ Claim(s) *19,29-31,37 and 42* ~~is/are allowed~~ are free of cited prior art

6)☒ Claim(s) *1-18,20-28,32-36,38-41,43 and 44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The response filed 15 April 2003 (Paper No. 9) as to amendment of claims 24, 28-31, 37 and 42, applicants' petition for extension of time of one month filed 15 April 2003 (Paper No. 8) have been entered. The pending claims 1-44 are under examination to the extent that they are drawn to the elected invention.

Note that the grounds of objection and/or rejection not explicitly stated and/or set forth below are withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claims 2, 8-13, 20-27and 43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 recites "by weight of the amino acids", which has not been defined in the specification; the recitation is unclear as to whether or not "the amino acids" refers to *a*) total amount of amino acid residues of a protein source, or *b*) total amount of free amino acids, or a combination of *a*) and *b*). See also claims 8, 20, 24 and 43. The dependent claims are also rejected.

Claim 32 is indefinite because the recitation "a daily recommended amount of threonine" is ambiguous without setting forth a subject to which the daily amount of threonine is recommended, *e.g.*, adult, child, or infant *etc.* or different animals because different age of the

subject and the species of animals, e.g., humans as opposed to other non-primate animals, require distinct/different recommended amount of threonine. See also claims 33 and 34.

The response to the rejection under 35 USC 112, the second paragraph

The response filed 15 April 2003 asserts that the claim term "by weight of the amino acid" is not indefinite as it is defined in the specification, page 9, lines 29-31 (see page 6, the fourth paragraph of the response). The argument is unpersuasive because nowhere in page 9 or throughout the specification has the recited term been defined.

The response argues that "a daily recommended amount of threonine" is clear as defined in page 8, lines 16-19 of the specification, and that although subject for daily recommended dosage may vary between different subjects, the dosage or requirement for threonine does not render the claims indefinite as the amount of threonine is based on the recommended dosage or requirement for threonine (see page 7, the second paragraph). The argument is not persuasive. The specification (page 8, lines 16-19) does not distinguish between different age group, e.g., infant and adult. Because the daily recommended dosage for adult may be lethal for infant, absent the factual indicia to the contrary, the skilled artisan would not be able to readily recognize what the recommended amount of threonine is suitable for the interest subject.

Claim Rejections - 35 USC §102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1 and 3-7 are rejected under 35 U.S.C. 102(e) as being anticipated by Demichele, S. J. (US Pat. No. 6468987).

Demichele *et al.* teach a method for treating ulcerative colitis (a intestinal inflammatory disease) comprising administering to a patient a nutritional product comprising a source of protein (see patent claim 29-33 and item *d* of patent claim 14), and teach that the diet has a significant impact on mucosal eicosanoid (glyco-moiety) biosynthesis (see column 10, lines 7-9). Further, as is evidenced in the specification on page 1, lines 18-20, and page 2, lines 3-8, where indicates a correlation of that ulcerative colitis disease state with an altered level of mucin production, and in view of the fact that mucin is a glycoprotein and incorporating eicosanoid lipid moieties into mucoprotein precursor is a part of mucin biosynthetic process, the Demichele method therefore refers to a treatment of the ulcerative disease state related to mucin level alteration.

Also, Demichele *et al.* teach the protein source comprises 75% whey protein (see column 17, line 54) and the protein is hydrolyzed (see claim 19). Since whey protein contains ~ 7.4% of

threonine by total weight of amino acid residues as evidenced by the specification at page 5, line 28-29, the threonine content would be 75% × 7.4% ≈ 5.6 %, which meets the limitations set forth in claims 3-4. Thus, the Demichele *et al.* teaching anticipates claims 1 and 3-4 of the instant application.

Further, Demichele *et al.* also teach the nutritional composition comprises lipid source and carbohydrate (see the patent claim 14, items *a* and *b*) and the composition comprising 10-50% medium chain triglycerides and 25-80% fish oil which is enriched in *Omega*-3 fatty acids that belongs to long chain triglyceride (see the patent claim 14). Thus, Demichele *et al.* anticipate claims 5-7 of the instant application.

The response to the rejection under 35 USC 102

The response filed 15 April 2003 asserts that Demichele et al. reference does not teach or suggest the disclosure set forth in claims 1 and 3-7, and that nutritional product, e.g., 75% whey protein is insufficient (see page 11). The argument is not persuasive. Claim 1 is directed to a method of treating a disease state with alteration to mucin level in a patient comprising enterally administering to the patient a nutritional composition comprising > 5.5% threonine. The claim limitation is met by the Demichele et al. teaching as to treating ulcerative colitis that is an evident disease with altered mucin production (see the statement *supra*).

Claim Rejections - 35 USC §103

Note that this is a new ground of rejection

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3-8, 14-18, 20, 22, 24, 28, 32-36, 38-39, 40-41 and 43-44 are rejected under 35 U.S.C. 103(a) as being obvious over Hennebicq-Reig *et al.* (*Biochem. J.* (1998) 334, 283-295) taken with Bertolo, R. F. P. *et al.* (*J. Nutr.* (1998) 128, 1752-1759), Demichele, S. J. (US Pat. No. 6468987), Pearson, G. R. et al. (*Vet. Record* (1987) 121, 557-559), and Granados, R. R. *et al.* (US Pat No. 6187558).

Hennebicq-Reig *et al.* teach importance of threonine for mucin synthesis (see Table 4), as applied to claims 1, 8, 14, 20, 24, 28, 32, 35 and 40 of the current application. Hennebicq-Reig

et al. do not expressly teach use of threonine or/and threonine rich nutritional composition for maintaining or increasing mucin, a major glycoprotein in gastric mucosa.

Bertolo et al. teach that administering threonine is necessary for maintenance of gut mucous coating as threonine requirement is proportional to mucin production, wherein mucin comprises large amount of threonine, i.e., accounted for > 40% of the amino acid residues of protein moiety of mucin, (see the second paragraph of the left column, page 1758).

Also, Bertolo *et al.* teach threonine is an essential amino acid for growing gut (see the right column, page 1758), wherein production of mucin protein is proportional to threonine requirement (see the second paragraph, page 1758), and wherein nearly 90% metabolizing threonine is incorporated into gastric mucosal protein, i.e., mucin, equivalent to 61% of dietary threonine is metabolized in gastrointestinal gust (see the paragraphs at the bridging pages 1757-1758). In addition, Bertolo *et al.* teach a process of administering total parenteral nutrition (TPN) that contains all the required nutrients including protein, threonine and other amino acids, fat, carbohydrates, vitamins, and minerals to a patient by employing the indicator amino acid oxidation technique, and that the TPN solution has the recommended threonine contents (see Materials and Methods section, the third paragraph). Thus, the Bertolo *et al.* teachings are applied to claims 8, 14, 24, 28 and 32 limitation of the current application.

Additionally, Bertolo *et al.* teach a process of administering to a patient threonine (see lines 3-6, the left column, page 1753, and experiments 1 and 2), and show a mean threonine requirement of 0.6 g/kg·day by measuring the concentration of the indicator amino acid (*i.e.*, the labeled Phenylalanine) at saturation level (see the 2nd paragraph, right column, page 1756, and Figure 5). The daily recommended threonine amount is given as 0.68 g /kg·day (see page 1756,

lines 1-6 form the bottom of the right column), then, the daily-recommended threonine amount would be 0.6/0.68 = 88%. The Bertolo et al. teaching is applicable to claims 8 and 32-33 of the current application.

Further, Bertolo et al. also teach that the ideal threonine/lysine ratio of 1: 1.54, *i.e.*, threonine is 9.09 g/kg diet *versus* lysine of 14.0 g/kg diet (see the last to second line of right column, page 1756); 9.09 g/kg diet then results in the value of 0.71 g/kg day calculated from 8.7 g/kg diet (~0.68 g/kg day) (see the 2nd paragraph, page 1756); thus, 0.71/0.68 = 1.04% should represent the % of a daily recommended amount of threonine, given that threonine/lysine ratio is 1:1.54, which meets the limitation of claim 34 of the current application.

Demichele *et al.* teach a method for treating ulcerative colitis (an intestinal inflammatory disease) comprising administering to a patient a nutritional product comprising a source of protein (see patent claim 29-33 and item *d* of patent claim 14), and teach that the diet has a significant impact on mucosal eicosanoid (glyco-moiety) biosynthesis (see column 10, lines 7-9). Since mucosal change is associated with ulceration in an animal, i.e., an altered mucin level is proportional to mucosal damage, i.e., ulceration, as taught by Pearson et al. (see "discussion" section), suggesting association of mucin alteration with ulceration disease state, the Demichele *et al.* teaching is applicable to the application claims 1, 20 and 35.

Also, Demichele *et al.* teach the protein source comprises 75% whey protein (see column 17, line 54) and the protein is hydrolyzed (see claim 19). Since whey protein contains ~ 7.4% of threonine by total weight of amino acid residues as evidenced by the specification at page 5, line

28-29, the threonine content would be 75% × 7.4% ≈ 5.6 %, which is applied to the limitations set forth in claims 3-4, 15-17, 22, 36 and 38-39, 41 and 43-44 of the current application.

Further, Demichele *et al.* also teach the nutritional composition comprises lipid source and carbohydrate (see the patent claim 14, items *a* and *b*) and the composition comprising 10-50% medium chain triglycerides and 25-80% fish oil which is enriched in *Omega*-3 fatty acids that belongs to long chain triglyceride (see the patent claim 14), the Demichele *et al.* teaching thus is applied to claims 5-7 and 18 of the instant application.

Demichele *et al.* does not teach treatment of bacterial infection comprising administering threonine rich composition.

Granados *et al.* teach the protective function of mucin in intestinal mucosal layer, and that mucin plays an active role in preventing bacterial infection of digestive tract (see column 1, lines 17-21 and 54-67). Additionally, Granados *et al.* teach that mucin is rich in threonine (see column 4, lines 42-52), as applied to claims 40-41 and 43-44.

One of ordinary skill in the art would have combined the teachings of Hennebicq-Reig *et al.* and Bertolo et al., because the teachings with respect to (*a*) threonine playing an essential role in maintaining mucin protein synthesis as taught by Hennebicq-Reig *et al.*, and (*b*) route and amount of administering threonine or/and nutrition composition comprising threonine as taught by Bertolo et al. would have led the skilled artisan to successfully arriving at the invention, i.e., a process of maintaining or increasing the synthesis of mucin in a patient as disclosed in claims 8, 14, 24, 28, 32-36 and 38-39.

Also, it would have been obvious for ordinary skill in the art to combine the teachings of Hennebicq-Reig et al., Demichele et al., Pearson, G. R. et al. and Granados et al., because (i) Hennebicq-Reig et al. teach that threonine is one of most important nutritional building blocks of mucin, (ii) Demichele et al. teach that the nutrition has a significant impact on mucosal glycoprotein synthesis, which comprises threonine-rich proteins, (*e.g.*, whey protein), lipids and carbohydrates, and teach a method of treating an intestinal inflammatory disease, i.e., ulcerative colitis which is associated with alteration of mucin synthesis as taught by Pearson et al., comprising administering to a patient a nutritional composition having protein(s) that comprises rich threonine content (e.g., whey protein); the Demichele teaching meets the claim limitation claims 1, 20, 22, 35-36 and 38-39), and (iii) Granados et al. explicitly teach that mucin plays an active role in preventing microbial infection of gastric mucosal layer (see column 1, lines 17-22, and column 4, lines 42-43) as applicable to claims 40-41 and 43-44 of the instant application. When combined the above teachings, the skilled artisan would have administered sufficient amount of threonine or threonine-rich nutritional composition to a subject for treating a disease associated with an alteration of mucin level. In addition, when combined, there would have been the following advantages: (*a*) the formulated nutrition can also be applied to young patients, as taught by Demichele *et al.* (see column 2, lines 61-65), and (*b*) threonine can be readily formulated with proteins, *e.g.*, whey protein, and other nutritional components, e.g., fatty acid and carbohydrate as taught by Demichele et al. (see the statement *supra*).

Therefore, the skilled artesian would have been motivated to combine the teachings of the above references with the above-stated advantages to develop a method of maintaining mucin synthesis or/and treating a disease state including intestinal bacterial infection or/and gastric

inflammation in a patient *via* administering a composition comprising threonine or/and threonine-rich nutritional supplement. Thus, the claimed invention was *prima facie* obvious to make and use at the time it was made.

Conclusion

Claims 1-18, 20-28, 32-36, 38-41 and 43-44 are rejected. Claims 19, 29-31, 37 and 42 are free of cited prior arts.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is (703) 306-3483. The examiner can normally be reached from 9:00 a.m. to 5:00 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Christopher Low, can be reached on 703 308-2923. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.

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June 3, 2003